Clinical Investigations

Effects of Statin Treatment on Cardiac Function in Patients With Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Whether additional benefit can be achieved with the use of statin treatment in patients with chronic heart failure (CHF) remains undetermined.

Hypothesis: Statin treatment may be effective in improving cardiac function and ameliorating ventricular remodeling in CHF patients.

Methods: The PubMed, MEDLINE, EMBASE, and EBM Reviews databases were searched for randomized controlled trials comparing statin treatment with nonstatin treatment in patients with CHF. Two reviews independently assessed studies and extracted data. Weighted mean differences (WMD) with 95% confidence intervals (CI) were calculated using random effects models.

Results: Eleven trials with 590 patients were included. Pooled analysis showed that statin treatment was associated with a significant increase in left ventricular ejection fraction (WMD: 3.35%, 95% CI: 0.80 to 5.91%, $P = 0.01$). The beneficial effects of statin treatment were also demonstrated by the reduction of left ventricular end-diastolic diameter (WMD: −3.77 mm, 95% CI: −6.24 to −1.31 mm, $P = 0.003$), left ventricular end-systolic diameter (WMD: −3.57 mm, 95% CI: −6.37 to −0.76 mm, $P = 0.01$), B-type natriuretic peptide (WMD: −83.17 pg/mL, 95% CI: −121.29 to −45.05 pg/mL, $P < 0.0001$), and New York Heart Association functional class (WMD: −0.30, 95% CI: −0.37 to −0.23, $P < 0.00001$). Meta-regression showed a statistically significant association between left ventricular ejection fraction improvement and follow-up duration ($P = 0.03$).

Conclusions: The current cumulative evidence suggests that use of statin treatment in CHF patients may result in the improvement of cardiac function and clinical symptoms, as well as the amelioration of left ventricular remodeling.

Introduction

Despite advances in therapy, chronic heart failure (CHF) remains a major cause of morbidity and mortality worldwide. CHF is associated with activation of oxidative stress, proinflammatory cytokines, and neurohormones.[1–3] In view of this, the class of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) was considered a promising candidate for the treatment of CHF, because statins exert diverse cellular, cholesterol-independent effects throughout the cardiovascular system encompassing enhancement of nitric oxide synthesis, improvement of endothelial function, inhibition of inflammatory cytokines, and restoration of impaired autonomic function.[4–6]

Previous experimental studies revealed that statins may attenuate pathologic myocardial remodeling and promote cardiac function in heart failure.[7,8] Thereafter, numerous trials were conducted to determine the beneficial role of statins on the failing myocardium in CHF patients; however, the results were conflicting. In order to provide a more robust estimate of the potential benefits of statin

Lei Zhang, MD, Shuning Zhang, MD, and Hong Jiang, MD, contributed equally to this work. This study was supported by the Key Projects in the National Science and Technology Pillar Program in the Eleventh Five-year Plan Period (No. 2006BAI01A04), National Natural Science Foundation of China (No. 30871073), National High-Tech Research and Development Program of China (No. 2006AA02A406), and Outstanding Youth Grant from National Natural Science Foundation of China (No. 30725036). This work was not funded by an industry sponsor. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Additional Supporting Information may be found in the online version of this article.

Received: June 9, 2010
Accepted with revision: June 22, 2010

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20821

treatment, we performed a meta-analysis of randomized controlled trials to evaluate the impact of statin treatment on cardiac function–related parameters in patients with CHF.

Methods

Search Strategy and Selection Criteria

We performed a literature search in the PubMed, MEDLINE, EMBASE, and EBM Reviews databases to July 2009. The search terms were "statin," "heart," "cardiac," "dysfunction," "insufficiency," "inadequacy," and "failure," without restrictions of language and publication form. The reference lists of studies that met our inclusion criteria was also searched for potentially relevant titles.

Studies were included in our analysis if they met the following criteria: (1) the design was a prospective, randomized controlled trial; (2) patients with established CHF, no matter the etiology, were assigned to statin treatment or control (nonstatin treatment or placebo) in addition to concurrent therapy; and (3) they reported data on left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), B-type natriuretic peptide (BNP), or New York Heart Association (NYHA) functional class.

Data Extraction and Quality Assessment

Two investigators independently reviewed all potentially eligible studies using predefined eligibility criteria and collected data from the included trials. Disagreements were resolved by consensus. We extracted details on study characteristics, patient characteristics, intervention strategies, duration of follow-up, and clinical outcomes including LVEF, LVEDD, LVESD, BNP, and NYHA functional class.

Quality assessments were evaluated with Jadad quality scale, and a numerical score between 0 and 5 was assigned as a measure of study design.

Data Synthesis and Analysis

All endpoints were based on the change from baseline to follow-up, and pooled effects were presented as weighted mean differences (WMD) with 95% confidence intervals (CI) using random effects models. Statistical heterogeneity was measured using the I^2 statistic ($I^2 > 50\%$ was considered representative of significant statistical inconsistency). Meta-regression and sensitivity analyses (including exclusion of 1 study at a time) were conducted to explore heterogeneity. Finally, on the basis of the data on LVEF, publication bias was tested using the Begg adjusted-rank correlation test and Egger regression asymmetry test. *P* values were 2-tailed, and the statistical significance was set at 0.05. All analyses were performed with Stata software 8.0 (StataCorp, College Station, TX).

Results

Selected Studies and Characteristics

The flow of selection of studies for inclusion in the meta-analysis is shown in Figure 1. Of the initial 4205 hits, 11 randomized controlled trials (RCTs) with a total of 590 patients satisfying the inclusion criteria were identified and analyzed.[9–19] One study by Smetanina et al[20] was excluded because no full text was available for data extraction and quality assessment. A summary of baseline characteristics of the included trials is shown in Table 1. No significant differences were seen between the groups assigned statins and placebo in background CHF therapies, including angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) and β-blocker therapy. Only 3 studies utilized rosuvastatin, cerivastatin, and simvastatin separately[10–12]; the rest of the included trials focused on atorvastatin.[9,13–19] Most of the patients enrolled in this meta-analysis had normal levels of low-density lipoprotein.[9–11,13–15,19] Additionally, 2 large-scale RCTs, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure (GISSI-HF) were excluded from this study due to lack of data on related endpoints.[21,22]

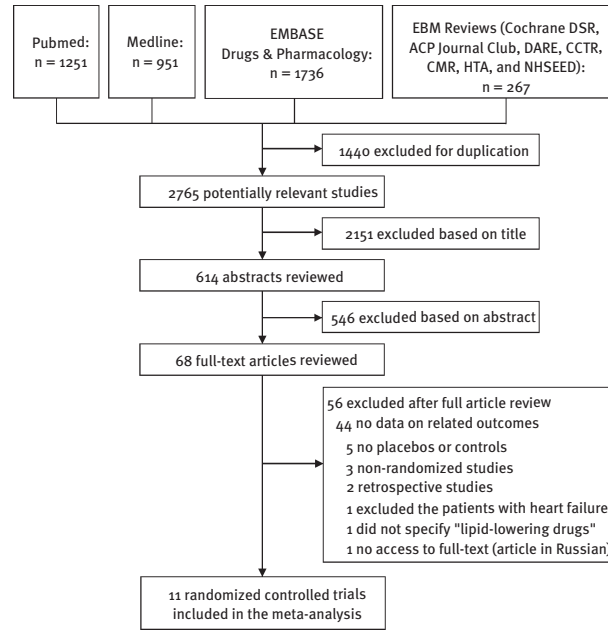

Figure 1. Search flow diagram for studies included in the meta-analysis.

Effects of Statin Treatment

The overall pooled results with random effects analysis showed that additional statin treatment was significantly superior to standard medical therapy in terms of LVEF improvement, with a clinically and statistically significant difference of 3.35% (95% CI: 0.80 to 5.91%, $P = 0.01$, I^2: 99.6%) (Figure 2A). Furthermore, statin therapy was similarly found to have benefits concerning LVEDD (WMD: −3.77 mm, 95% CI: −6.24 to −1.31 mm, $P = 0.003$, I^2: 99.0%) (Figure 2B); LVESD (WMD: −3.57 mm, 95% CI: −6.37 to −0.76 mm, $P = 0.01$, I^2: 97.2%) (Figure 2C); BNP (WMD: −83.17 pg/mL, 95% CI: −121.29 to −45.05 pg/mL, $P < 0.0001$, I^2: 96.3%) (Figure 3A); and NYHA functional class (WMD: −0.30, 95% CI: −0.37 to −0.23, $P < 0.00001$, I^2: 72.4%) (Figure 3B), as compared with control. All these

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DOI:10.1002/clc.20821

Table 1. Characteristics of 11 Clinical Trials Included in the Meta-analysis

Authors	Publication Year	No. of Patients	Mean Age, y	Male,%	Ischemic Etiology, %	NYHA Class	Mean LVEF, %	Statin Type, Dose	Follow-Up, mo	Jadad Score
Bleske et al[9]	2006	15	56	60	0	I-III	25	Atorvastatin, 80 mg/d	3	4
Krum et al[10]	2007	86	62	80	12	II-IV	29	Rosuvastatin, 10–40 mg/d	6	2
Laufs et al[11]	2004	15	51	NA	0	II-III	42	Cerivastatin, 0.4 mg/d	5	3
Node et al[12]	2003	48	54	71	0	II-III	34	Simvastatin, 5–10 mg/d	3.5	3
Sola et al[13]	2006	108	54	62	0	II-IV	33	Atorvastatin, 20 mg/d	12	3
Strey et al[14]	2006	23	61	70	0	II-III	30	Atorvastatin, 40 mg/d	1.5	3
Tousoulis et al[15]	2005	26	69	100	100	III-IV	26	Atorvastatin, 10 mg/d	1	2
Vrtovec et al[16]	2005	76	67	54	62	III	24	Atorvastatin, 10 mg/d	3	2
Wojnicz et al[17]	2006	74	38	81	0	II-III	28	Atorvastatin, 40 mg/d	6	3
Xie et al[18]	2008 (epub)	81	NA	NA	100	II-IV	38	Atorvastatin, 10 mg/d	12	1
Yamada et al[19]	2007	38	64	79	53	I-III	34	Atorvastatin, 10 mg/d	31	5

Abbreviations: LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association.

findings suggest that statin treatment can improve cardiac function as well as ameliorate cardiac remodeling.

Meta-Regression and Sensitivity Analysis

Because of the statistical heterogeneity across the enrolled studies, several exploratory meta-regression analyses were performed to appraise the impact of different covariates on the changes in LVEF associated with statin treatment. Specifically, we did not find statistically significant association between the benefits of statin treatment and year of publication ($P = 0.81$), patient age ($P = 0.18$), patient sex ($P = 0.57$), CHF etiology ($P = 0.44$), and baseline LVEF ($P = 0.08$). However, we found a statistically significant association between follow-up duration and LVEF improvement ($P = 0.03$), suggesting the heterogeneity could at least partially be accounted for by the difference in follow-up duration, and a linear relationship between them is shown in Figure 4. With respect to other endpoints (LVEDD, LVESD, BNP, and NYHA functional class), meta-regression was not performed because of inadequate power due to the low number of studies.

Subsequently, sensitivity analysis excluding 1 study at a time confirmed in direction and magnitude of statistical significance the results concerning BNP and NYHA functional class. Nevertheless, we found that the beneficial effect of statin treatment on LVEF turned to be vague (WMD: 2.62%, 95% CI: 0.08–5.33, $P = 0.06$) when the study by Yamada et al[19] was omitted. Likewise, the impact of statin treatment on LVEDD and LVESD vanished simultaneously when studies conducted by either Sola et al[13] (LVEDD—WMD: −2.30 mm, 95% CI: −5.22 to 0.62 mm, $P = 0.12$; LVESD—WMD: −2.88 mm, 95% CI: −7.33 to 1.57 mm, $P = 0.20$) or Wojnicz et al[17] (LVEDD—WMD: −3.17 mm, 95% CI: −7.92 to 1.59 mm, $P = 0.19$; LVESD—WMD: −2.74 mm, 95% CI: −6.72 to 1.24 mm, $P = 0.18$) were excluded, but the favorable tendency remained.

Publication Bias

Assessment of publication bias using Egger's and Begg's tests showed that no potential publication bias existed among the included trials (Egger's test: $P = 0.14$; Begg's test: $P = 0.47$) (Supporting Figure 1A, 1B).

Discussion

We performed this meta-analysis of 11 RCTs to determine the beneficial effects of statin treatment in patients with CHF. Interestingly, the results showed that in CHF patients, statin treatment significantly increases LVEF as compared with control. Moreover, its beneficial effects were further demonstrated by decreasing LVEDD, LVESD, BNP, and NYHA functional class. For assurance, we performed Egger's and Begg's tests to exclude the influence of publication bias on overall analyses.

Contrary to many earlier studies, 2 large-scale randomized controlled trials, Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) and Effect of Rosuvastatin in Patients with Chronic Heart Failure (GISSI-HF), failed to show the expected benefits of statin treatment in patients with CHF[21,22]; nevertheless, 2 subsequent post hoc analyses for the CORONA study, which were inconsistent with our findings, inversely confirmed the potential benefits of statin treatment in a proportion of the patients with CHF (patients with high-sensitivity C-reactive protein $\geq$2.0 mg/L, or plasma amino-terminal pro-brain natriuretic peptide<868 pg/mL).[23,24] That is to say, the benefits of statin treatment in patients with CHF cannot yet be completely denied.

The well-established benefits of statins are thought to be mediated through their lipid-lowering properties that decelerate the progression of the underlying cardiovascular diseases, such as decreasing the incidence of CHF in hyperlipidemic patients and reducing subsequent ischemic cardiac events.[25] However, we should note that most of the subjects enrolled in our meta-analysis had normal levels of low-density lipoprotein[9–11,13–15,19]; the aforementioned

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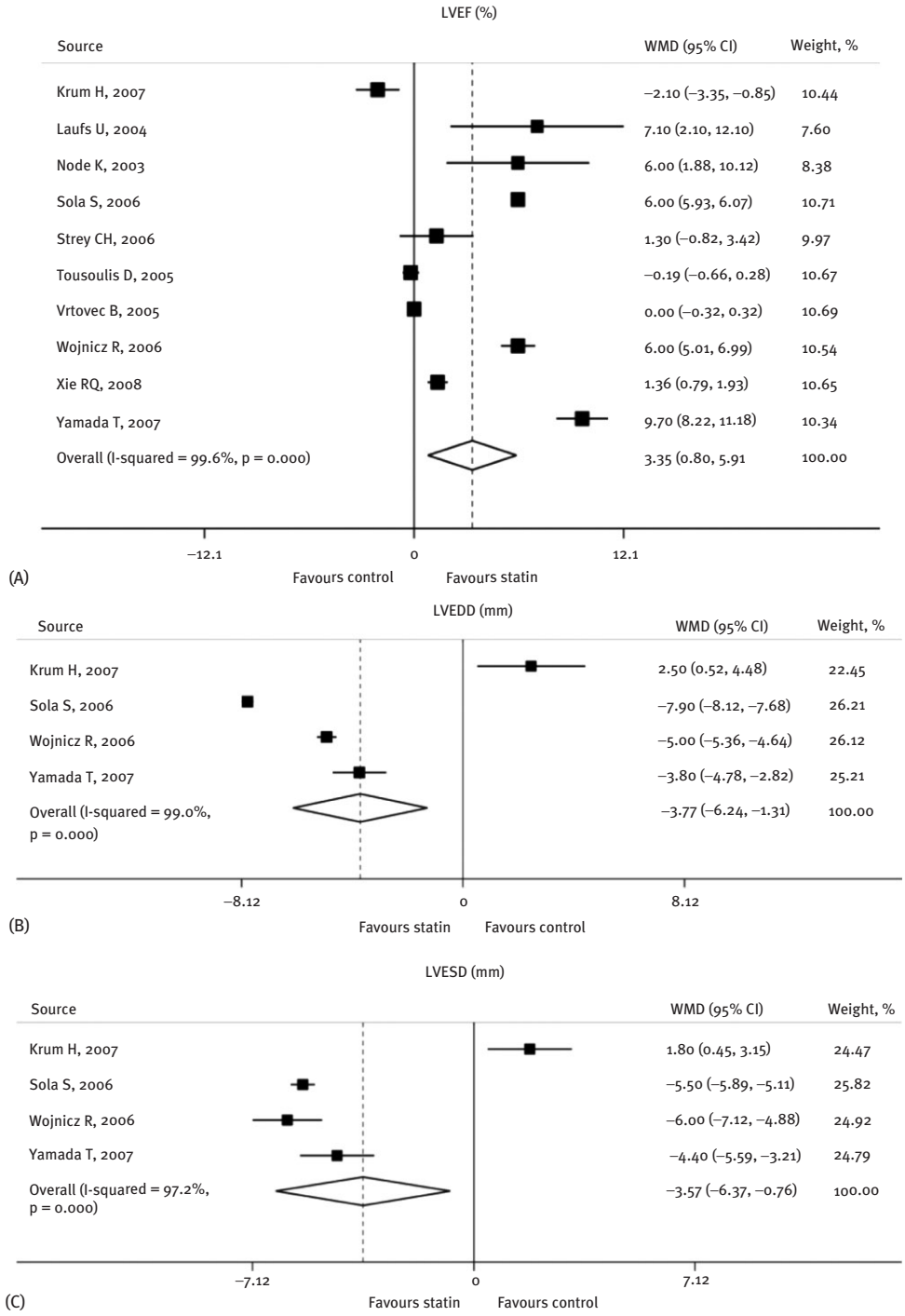

Figure 2. LVEF (%) (A), LVEDD (mm) (B), and LVESD (mm) (C) during follow-up in patients randomized to statin treatment vs nonstatin treatment with WMDs and 95% CIs. The effect size of each study is proportional to the statistical weight. The diamond indicates the overall summary estimate for the analysis; the width of the diamond represents the 95% CI. Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; WMD, weighted mean difference. Continued on next page.

benefits of statins in CHF patients might, therefore, be accounted for by many other favorable pleiotropic effects. Currently, multiple studies have revealed that statins can decrease vascular and myocardial oxidative stress, facilitate nitric oxide synthesis and improve endothelial function, along with reducing markers of inflammation and cytokine activation,[26–29] all of which are thought to be important in mediating the progression of heart failure.[28,30,31] In addition, statins possess antihypertrophic and antifibrotic effects that would also be expected to benefit cardiac remodeling and cardiac function and thereby ameliorate clinical symptoms represented by NYHA functional class.[26,32,33]

DOI:10.1002/clc.20821

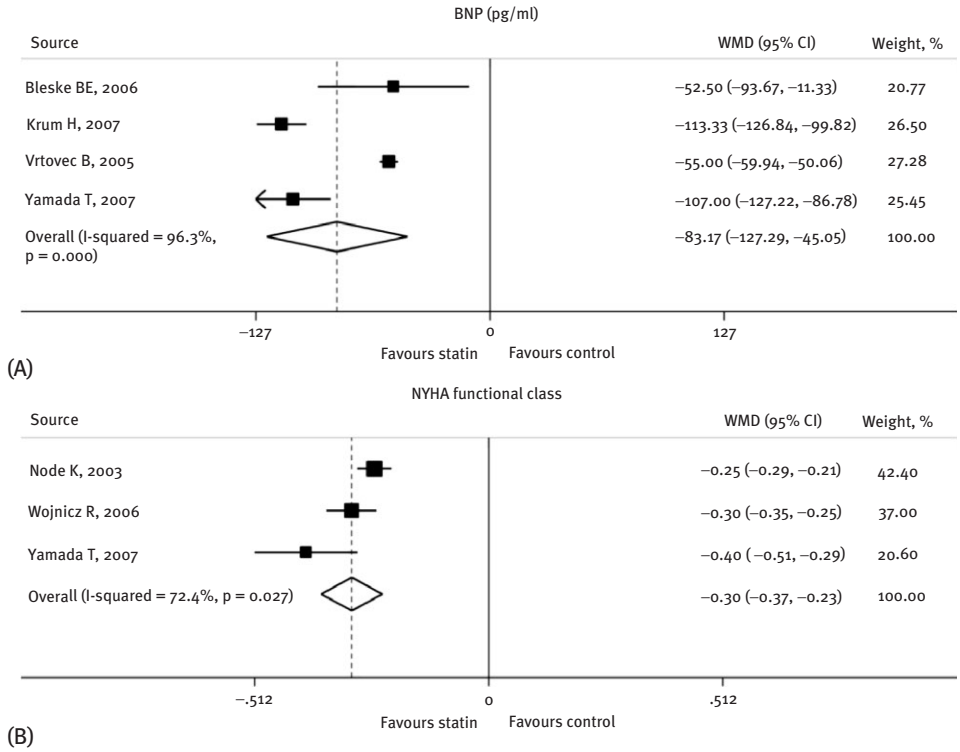

Figure 3. BNP (pg/mL) (A) and NYHA functional class (B) during follow-up in patients randomized to statin treatment vs nonstatin treatment with WMDs and 95% CIs. The effect size of each study is proportional to the statistical weight. The diamond indicates the overall summary estimate for the analysis; the width of the diamond represents the 95% CI. Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; NYHA, New York Heart Association; WMD, weighted mean difference.

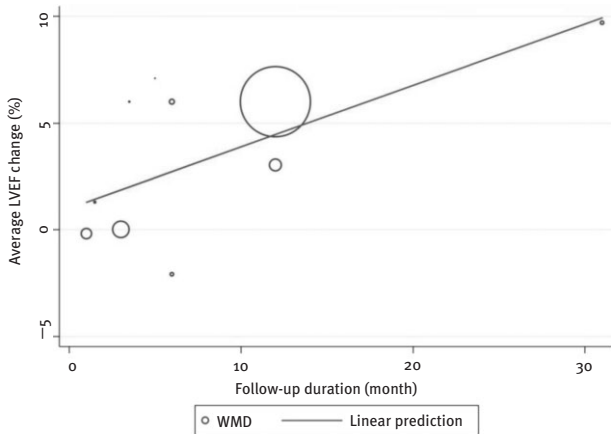

Figure 4. Meta-regression between follow-up duration and LVEF improvement ($P = 0.03$). This trend supports the presence of a time-dependent relationship (size of circle is proportional to size of trial). Abbreviations: LVEF, left ventricular ejection fraction; WMD, weighted mean difference.

Specifically, it is possible that statins improve cardiac function in patients with CHF partially by exerting inhibitory effects on matrix metalloproteinases.[34,35] Thus, combining these findings with the fact that the change of BNP level is negatively related to the alteration of cardiac structure and function,[36,37] it seems plausible that statins can, as well, down-regulate the blood level of BNP, which provides powerful prognostic information in patients with CHF.[38]

Because the beneficial effects of statin treatment in CHF patients were accompanied by significant heterogeneity in this pooled analysis, we performed plenty of meta-regression analyses to explore potential sources. The results showed that, unlike publication year, mean age, sex, etiology of CHF, and baseline LVEF, follow-up duration was significantly associated with LVEF improvement, whereas longer treatment intervals tended to yield more clinical benefits. In other words, the difference in follow-up duration might be an origin of the interstudy discrepancy regarding the clinical outcome of LVEF. Because of the existing relationship between follow-up duration and LVEF, it is not difficult to understand the equivocal results in sensitivity analyses. For instance, the study by Yamada[19] had a much longer follow-up of 31 months, as compared with an average of 8.4 months follow-up in this meta-analysis; thus, the beneficial effects of statin treatment are likely to be concealed by omitting this study from the overall analysis.

Besides follow-up duration, another possible contributor to the conflicting results among the included studies could have been the utilization of different statins. Previous studies have verified the drug-specific effects of statins.[39,40] Similarly, we noticed that only 1 study[10] in this meta-analysis focused on rosuvastatin treatment in CHF patients, and it failed to show any beneficial effects on cardiac function and remodeling; whereas other enrolled studies[9,11–19] that targeted atorvastatin, cerivastatin, or simvastatin have brought about relatively better outcomes. This suggests

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DOI:10.1002/clc.20821

that statins may not be acting as a "class," at least in patients with CHF.

As with many other meta-analyses, this study has several limitations. It is worth noting that, although 11 RCTs were included in this meta-analysis, these trials were relatively small, with only 590 subjects in all; also, the enrolled studies had wide-ranging follow-up duration. Both of these factors may result in unreliable outcomes. In addition, even though the findings from this meta-analysis are highly suggestive, we have not yet determined whether additional use of statins would reduce mortality in patients with CHF.

Conclusion

This meta-analysis showed that statin treatment might confer benefits not only in increasing LVEF, but also in reducing LVEDD, LVESD, BNP, and NYHA functional class in CHF patients. Moreover, the improvement of LVEF associated with statin treatment might be time-dependent, suggesting that statin therapy may be a potential novel treatment strategy for CHF patients.

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